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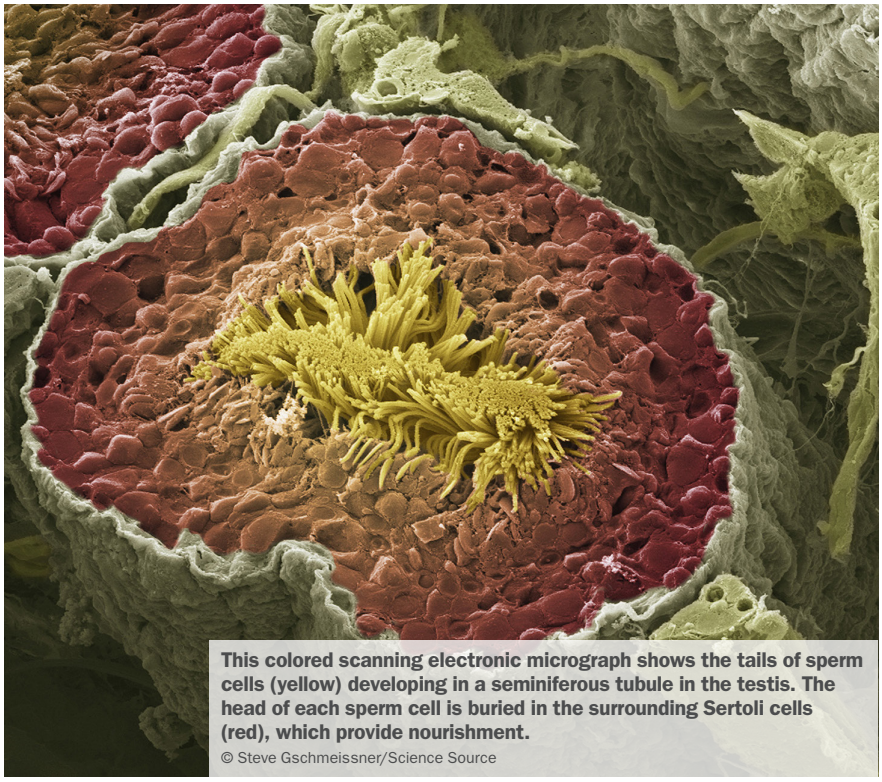
Comparing Models

DBP Effects in Rat and Human Germ Cells

Prenatal exposure to di(*n*-butyl) phthalate (DBP), a chemical that makes plastics flexible, has been associated with a spectrum of male reproductive system disorders in animals,[1] and there is evidence it may adversely affect human testicular germ cells.[2] A new study in *EHP* provides new evidence regarding mechanisms of DBP-related effects in germ cells and suggests that a rat model may be suitable for studying effects of DBP on human germ cells.[3]

Testicular tissue includes Leydig cells, which produce androgenic hormones, and Sertoli cells, which form the structure of the seminiferous tubules and support the production and maturation of the germ cells that develop into sperm.[4] Prenatal exposure to certain endocrine-disrupting agents may interfere with Leydig cell function and derail androgen-directed development of the male reproductive system.[5] A potential outcome of this disruption is testicular dysgenesis syndrome (TDS), characterized by genital abnormalities at birth and by impaired sperm production and increased testicular cancer risk in adulthood.[5]



This colored scanning electronic micrograph shows the tails of sperm cells (yellow) developing in a seminiferous tubule in the testis. The head of each sperm cell is buried in the surrounding Sertoli cells (red), which provide nourishment.

There is some evidence that TDS-related disorders have increased in the last several decades, which some investigators hypothesize may have been caused by endocrine-disrupting compounds.[6] Animal experiments suggested DBP to be one such compound, but the compound had no effect on androgen production by human fetal Leydig cells.[5,7] However, germ cell anomalies, possibly due to DBP-related effects on Sertoli cells, have been observed in fetal rat and mouse testes as well as samples of fetal human testis xenografts (testicular tissue implanted under the skin of mice).[2,6] A new line of inquiry is investigating how these anomalies occurred and whether they are comparable between species.

The current study focused on three previously suggested germ cell anomalies: abnormal clustering, or aggregation, of germ cells; germ cells with multiple nuclei (termed multinucleated gonocytes; MNGs); and reduced numbers of germ cells. Any of these anomalies would signal some error in germ cell formation or maturation.

In one set of experiments, pregnant rats received DBP at 0, 4, 20, 100, or 500 mg/kg daily, beginning on embryonic day 13.5 (e13.5). The testes of male offspring, collected on e17.5, e21.5, and postnatal day 4, were examined microscopically to identify and enumerate cell types, determine the developmental stage of germ cells (undifferentiated or differentiated), and evaluate interactions between Sertoli cells and germ cells. One testis from each e21.5 male fetus was analyzed for the expression of the genes for these components. In a separate set of experiments, mice bearing human fetal testis xenografts were dosed with DBP at 0 or 500 mg/kg daily for 3 weeks, after which the xenografted samples underwent the same analyses as those from the rats.

DBP exposure was associated with similar effects in rat and human samples, although to a lesser extent in human tissue, with aggregation being particularly rare in the xenografts. Reduced numbers were more common among undifferentiated germ cells, whereas aggregation and MNGs tended to occur more among differentiated germ cells. The aggregation appeared to arise from diminished Sertoli–germ cell interaction, but gene expression was normal.[3]

A particular strength of this study was its focus on effects on the seminiferous cords, which were similar in rat and human tissue. "This study highlights that attention should be shifting towards the seminiferous cord effects of phthalate exposure during development," says Kim Boekelheide, a professor of pathology and laboratory medicine at the Brown University School of Medicine, who was not involved in the study. "I think this article points that out nicely and suggests some tools that can be used to look at those effects."

The implications of the current results for human health are unclear, however. "Although our results show small effects of DBP on germ cells in the human fetal testis, none of these effects are directly relevant to the origins of testis germ cell cancer insofar as we presently understand this," says study coauthor Sander van den Driesche, a senior postdoctoral fellow at the MRC Centre for Reproductive Health in Edinburgh. "Regarding fertility, effects on germ cells in fetal life can have impacts in adulthood," he says. However, he notes that such effects in rats are related to DBP-induced suppression of testosterone production, which as previously noted, may not occur in the human fetal testis.

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